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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/011,940	03/03/99	NAUCK	M 864861USWO

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FOLEY & LARDNER
3000 K STREET, N.W. STE.500
WASHINGTON DC 20007-5109

EXAMINER	
CELSA, B	
ART UNIT	PAPER NUMBER
1627	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Office Action Summary

Application No.	Applicant(s)
09/011,940	Nauck et al.
Examiner	**Group Art Unit**
Bennett Celsa	1627

☒ Responsive to communication(s) filed on *Amendment dated 12/1/00 in paper no. 18* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 2, 17-26, 28-39, and 41-50* is/are pending in the application.

Of the above, claim(s) *26, 28-31, and 36-39* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 17-25, 32-35, and 41-50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 12/1/00 in paper no. 18 is hereby acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1-2, 17-26 and 28-39 and 41-50 are currently pending.

Claims 26, 28-31 and 36-39 are withdrawn from consideration as being directed to a nonelected invention.

Claims 1-2, 17-25, 32-35 and 41-50 are currently under consideration.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's amendment has overcome the objection of claims 49-50 under 37 CFR 1.75(c), as being of improper dependent form.

Applicant's amendment has overcome the new matter rejections of claims 21 and 47-48.

The anticipation rejection over the Habener, U.S. Pat. No. 5,118,666 (6/92) was found partially persuasive. A new rejection was directed to that portion of the Habener teaching which was specifically directed to an example, not addressed by applicant's representative.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

2. Claims 20, 21, 41 and 44 (and claims dependent thereon) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. The new limitation of claim 21, e.g. "are administered at a rate of 0.01 ... per minute" constitutes new matter to extent that these recited amounts encompass parenteral administration means other than "infusion". In other words, the specification only provides support for this limitation with respect to administration by infusion.

B. The new limitation in claims 41 and 44 directed to "organic molecular mimics ... receptor sites" constitutes new matter to the extent that this limitation goes beyond "small organic molecular mimics ... receptor sites" which is recited in the specification.

C. To the extent that claim 20 is directed to a range of "nutrients' that is broader that "a source of carbohydrate nutrients" which elicits the claimed glucose sugar level, the increase in scope of the range of blood sugar to any nutrient constitutes new matter.

3. Claims 20, 41 and 44 (and claims dependent thereon) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 20, "the source of carbohydrate nutrients" lacks clear antecedent basis.

B. In claims 41 and 44, the phrase " (small, medium or big)organic molecular mimics of the insulinotropic peptides which fit the insulinotropic receptor sites" since there is no metes and bounds regarding the chemical structure of the "mimics", other than the presence of carbon. Additionally, the term "**mimics** of the insulinotropic peptides" and the term "fit the insulinotropic receptor sites" are indefinite since "mimicry" is a "relative" term and the type of "mimicry" (structural, conformation, physical or otherwise) , degree of mimicry (50% ? 80% etc) and means of measuring mimicry is not disclosed nor defined in the specification.. Additionally, what constitutes "**fitting** a receptor site" (is mere binding enough), the degree of fit, and the means of measuring fit is not described nor defined in the specification. It is additionally noted that the term "**small** organic molecular mimics..." disclosed in the specification also represents the use of a relative term (e.g. "small"). The use of relative terminology in a claim is indefinite since this terminology is not defined by the claim; nor does, the specification provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

4. Claims 41 and 44 (and claims dependent thereon) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Lack of Written Description)

The presently claimed invention is directed to the use of "organic molecular mimics of the insulinotropic peptides which fit the insulinotropic receptor sites" wherein "insulinotropic peptides" are defined as in the claim (e.g. GLP 1, GLP (7-34,35,36,37), fragments, substitution analogs and ketones, carboxamides, esters etc.) .

The scope of "mimics" (big, small or otherwise) which are "organic" is unduly broad, since there is no metes and bounds regarding the chemical structure of the "mimics", other than the presence of carbon. Additionally, the term "**mimics** of the insulinotropic peptides" and the term "fit the insulinotropic receptor sites" are indefinite since "mimicry" is a "relative" term and the type of "mimicry" (structural, conformation, physical or otherwise) , degree of mimicry (50% ? 80% etc) and means of measuring mimicry is not disclosed nor defined in the specification.. Additionally, what constitutes "**fitting** a receptor site" (is mere binding enough), the degree of fit, and the means of measuring fit is not described nor defined in the specification. It is additionally noted that the term "**small** organic molecular mimics..." disclosed in the specification also represents the use of a relative term (e.g. "small"). The use of relative terminology in a claim is indefinite since this terminology is not defined by the claim; nor does, the specification provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In support of an unduly large and indefinite generic of "mimics" as presently claimed, the present application fails to describe an example of a single peptide which is within the scope of the presently claimed invention.

Applicant's claimed scope of compounds for therapeutic use represents an invitation to experiment regarding possible peptide compounds selected from among a pool of billions of "organic" compounds which may be peptidic or non-peptidic in structure.

The unpredictability of ligand receptor binding is known in the art. . Additionally, the effects, a priori, of nonconservative substitutions which differ sterically and/or hydrophobically on substrate/ligand binding is unpredictable; for substrate/ligand binding is stereospecific for a peptide/protein of the proper conformation ie. three dimensional structure. Additionally, the conformation of different viral substrates would be expected to differ in an unpredictable manner. Length and amino acid composition affects the three dimensional nature of a given peptide.

With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope, both possess the alleged utility and additionally demonstrate that *applicant had*

possession of the full scope of the claimed invention. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Unlke *Lilly*, applicant **does not** HAVE A SINGLE EXAMPLE of a peptide within the scope of the presently claimed invention and thus does not provide even a single peptide species in support of a potentially broad generic of different and nonexemplified sequences (e.g. substitute C-DNA in Lilly with peptides) which generic is much broader than the Lilly generic invention.

Unlike Lilly, there is NO means of obtaining or testing these "organic" mimic compounds.

Accordingly, it is clear that applicant has not demonstrated possession of the scope of the presently claimed subject matter. In fact applicant, in the present case, unlike the Lilly case, *has failed to demonstrate even a single species within the scope of the presently claimed generic.* Accordingly, applicant is not in possession of the presently claimed invention.

5. Claims 41 and 44 (and claims dependent thereon) are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which:

a. Lacks essential subject matter (e.g. See *Ex parte Bhide* cited below); AND

b. Is not enabling for both making and use.

The unpredictability of ligand receptor binding is known in the art. . Additionally, the effects, a priori, of nonconservative substitutions which differ sterically and/or hydrophobically on substrate/ligand binding is unpredictable; for substrate/ligand binding is stereospecific for a peptide/protein of the proper conformation ie. three dimensional structure. Length and amino acid composition affects the three dimensional nature of a given peptide.

Accordingly, the material composition (e.g. epitope(s)) of the ligand which is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). In this regard, it is noted that claims which lack critical or essential subject matter which is necessary to the practice of the invention, but is not included in the claim(s), including essential compound structure, . is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); and *Ex Parte Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441.

Turning to enablement is it noted that claims, as written, fails to recite the material composition of the ligand; only that it is an "organic molecular mimics of the insulinotropic peptides which fit the insulinotropic receptor sites" wherein "insulinotropic peptides" are defined

as in the claim (e.g. GLP 1, GLP (7-34,35,36,37), fragments, substitution analogs and ketones, carboxamides, esters etc.) .

As such, with respect to the claims, the specification fails to adequately provide guidance or examples of "how to make and use" all the molecules that would serve as organic mimics (e.g.ligands or otherwise), whether derived or not derived from the claimed insulinotropic peptides commensurate in scope with the claims in the absence of undue experimentation because the requisite chemical composition having the necessary structural (polypeptide or othewise) and/or functional properties (e.g. Size, structure, conformation, receptor "fit", degree and/or type of mimicry etc) are not defined by what they are, but in fact by what they are not, which is insufficient to distinguish the "mimic" in such a way that the testing of an inordinate number of "organic" compounds (known and unknown) could be circumvented.

6. Claims 1-2, 17-18, 21-25, 32-33, 35 and 41, 44, 45, 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Habener, U.S. Pat. No. 5,118,666 (6/92)

Habener '666 discloses the administration (e.g. perfusate) of a composition comprising GLP-1 (7-37) and/or GLP-1 (8-37) with glucose in a rat (e.g. a patient) which achieves "plateau" insulin sustained release (e.g. see Example 9).

Outstanding Objection (s) and/or Rejection (s)

7. Claims 1-2, 17-19, 21-25, 32-35 and 41-48 are rejected under 35 U.S.C. 102(e) as being anticipated by Habener, U.S. Pat. No are rejected under 35 U.S.C. 102(b) as being anticipated by Habener, U.S. Pat. No 5,614,492 (3/97: filed 9/91 or earlier).

Habener "492 disclose the use of GLP 1 and its derivatives (e.g. col. 7) to treat both diabetes and hyperglycemia (e.g. see col. 6, lines 1-10) due to the peptide's "insulinotropic" activity (e.g. see col. 5, line 60-70). "Parenteral administration" of GLP 1 and its derivatives in pharmaceutical compositions comprising carbohydrates (e.g. lactose), polyamino acids: controlled release formulations comprising lipid derivatives (e.g. liposomes) e.g. see bottom of col. 9 to top of col. 10) as well as conjugates thereof (e.g. see col. 10, lines 13-26) anticipate the presently claimed invention. Further Example 11 (e.g. col. 21-28, especially "meal studies") disclose the administration of GLP-1 both during a meal (e..g 50% CHO; 30% fat; 20% protein: see e.g. col. 22, lines 55-67) and postprandial to both NORMAL and non-diabetic patients with the successful control of plasma glucose levels. See also patent claims 1 and 9 (and dependent claims thereon) teaching the use of GLP-1 and derivatives to treat diabetes and hyperglycemia.

Accordingly, the parenteral administration of GLP-1 and its derivatives before/during/after meals that both contained and generated CHO (e.g. especially glucose) anticipates the presently claimed invention. See also patent claims which additionally disclose the treatment of both diabetes and hyperglycemia utilizing GLP-1 containing compositions.

Discussion

Applicant's arguments directed to the above anticipation rejection were considered but deemed nonpersuasive for the following reasons.

Initially it is noted that the above rejection were modified to incorporate the patent claim teaching of the above reference.

Applicant argues that the Habener reference's pointing out that "contaminants" (col. 9, line 25) obviates anticipation and thus only teaches the use of lactose which is not present in nutritionally effective amounts.

However, applicant is clearly not reading the reference as a whole since, as pointed to in the rejection above. See e.g. Example 11 (and patent claims) which clearly anticipate the use of nutrients with GLP-1 and its derivatives.

Accordingly, the rejection, as modified, is hereby maintained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2, 17-25, 32-35 and 41-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Specification disclosure as to the state of the prior art in view of Habener, U.S. Pat. No. 5,614,492 (3/97: filed 9/91 or earlier) and/or Eng US Pat. No. 5,424,286 (6/95) .

The specification on pages 1-2 and page 10, lines 15 describes the state of the prior art regarding the necessity for providing parenteral nutrition to patients having "disturbed glucose metabolism" (e.g. surgery patients, shock etc) as well as to malnourished patients while overcoming the hyperglycemia that accompanies parenteral nutrition. Coadministration of insulin with parenteral nutrition in order to overcome the hyperglycemia problem has its drawbacks (e.g. see page 1, lines 13-25).

The State of the Prior Art as described in the specification differs from the presently claimed invention which incorporates the use of "insulinotropic peptides" (e.g. GLP-1 and its derivatives) in parenteral nutrition compositions which comprise nutrients (e.g. glucose or glucose generating compounds) for alimentary nutrition or to treat hyperglycemic states.

However, both the Habener and Eng Patent references teach the "insulinotropic" nature of GLP-1 and related peptides e.g. the ability of these peptides to endogenously generate insulin and thus combat hyperglycemia. Additionally, the prior/sequential and co-administration of these

"insulinotropic" peptides with a meal containing nutrients (e.g. which include glucose or generate glucose) and the peptides concomitant ability to obtain normalized glucose levels is both disclosed and suggested by the Habener and/or Eng patents (e.g. see Habener, Example 11, col. 21-28 and patent claims addressing treatment of diabetes and hyperglycemia; e.g. see Eng at col. 1, lines 49-67 disclosing lowering of meal-related glucose levels by parenteral administration of GLP-1 and GLIP which effect was also found with other "insulinotropic" peptides (e.g. exendins) alone or in combination (including sequential) with GLP-1 (e.g. see Eng col. 2, lines 35-40; col. 5, lines 14-20; Example 2 (col. 6-7); Example 5 relating to diabetics; and patent claims 5-6.

The determination of optimal amounts of "insulinotropic" peptides and/or nutrients taken sequentially or in combination is well within the skill of the art as well as the determination of optimal delivery formulations (e.g. tablets, pills, delayed release etc.) and time of delivery (e.g. coadministered, sequential etc.).

One of ordinary skill in the art would be motivated to substitute the "insulinotropic" peptides disclosed by the Eng or Habener references for insulin in "parenteral" formulations as disclosed in the Specification, due to the problematic use of insulin as discussed in the specification and in view of the ability of "insulinotropic peptides" to endogenously produce insulin as taught by the Eng and/or Habener references.

Accordingly, the incorporation of "insulinotropic" peptides (e.g. GLP-1 or its derivatives) into parenteral formulations containing "nutrients" to treat diabetics, non-diabetics (e.g. hyperglycemia) or malnourished individuals would have been obvious to one of ordinary skill in

the art at the time of applicant's invention in view of the Habener and/or Eng references which demonstrate that administration of these peptides to obtain normalized glucose levels; regardless of the cause of hyperglycemia (meal/diabetes/hyperglycemia etc.).

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant separately argues that the Eng and Habener patent references teach that the mere presence of category of impurities (e.g. peptide, CHO etc.) present in the formulation of the GLP-1 or its derivatives is a teaching away from the use of nutrients combined with GLP-1.

Applicant's arguments are not persuasive since applicant fails to address the Eng and Habener teachings as a whole which suggest the administration (e.g. non-alimentary) of "insulinotropic" peptides (e.g. exendins and GLP-1 and its derivatives) to treat hyperglycemia and diabetes alone and in conjunction with nutrients (e.g. Habener examples 9 and 11).

It is also noted that applicant has failed to address the teaching of the specification with the above Eng and Habener references.

Accordingly, the above obviousness rejection is hereby maintained.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

March 19, 2001

BENNETT CELSA
PRIMARY EXAMINER